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Parvalbumin 阳性中间神经元缺陷在精神分裂症病理机制中的作用*

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摘 要 精神分裂症是一种多发于青壮年的重性精神病, 其原因尚不明确。经典的多巴胺缺陷理论假说在某些方面欠缺解释力; 与此同时, 关于 Parvalbumin 阳性的中间神经元(后简称 PV+神经元)缺陷在精神分裂症病理机制中的作用逐渐明晰, 并引起了越来越多的关注。PV+神经元在绝大部分脑区中是一种快速放电的抑制性神经元, 参与了突触可塑性的调节, 兴奋/抑制平衡的维持和神经发生等。而在精神分裂症中, PV+神经元的异常在患者和动物研究中都被普遍证实, 并发现与 NMDA 受体缺陷、gamma 波异常和氧化应激存在某些关联。

关键词 精神分裂症; 中间神经元; NMDA 受体; 氧化应激

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1 前言

精神分裂症是一种重性精神病, 多在青壮年时期发作, 是世界上十大致残或使人丧失劳动能力的疾病之一, 同时也是各种精神疾病中患病率最高的一种, 其临床表现症状各异, 涉及感知觉、思维、情感和行为等多方面的障碍以及精神活动的不协调, 包括幻想、妄想、偏执和/或精神错乱等阳性症状, 以及持续的进行性的感情淡漠、注意力不集中、社交回避、认知缺损等阴性症状。

目前精神分裂症产生的病因并不十分明确, 科学家们通过临床用药经验和各种实验证据来探索精神分裂症产生的原因, 进而提出各种假说, 主要包括: 多巴胺系统功能亢进假说(Davis & Kahn, 1991; Howes & Kapur, 2009)、γ-氨基丁酸(GABA)系统缺陷导致的兴奋/抑制不平衡假说(Lewis, Hashimoto, & Volk, 2005)、NMDA (N-methyl-D- aspartic acid)受体缺陷假说(Jentsch & Roth, 1999; Tsai & Coyle, 2002)以及 5-羟色胺(5-HT)受体异常假说等等(Breier, 1995; Abi-Dargham, Laruelle, Aghajanian, Charney, & Krystal, 1997)。其中, 多巴胺假说基于经典的多巴胺受体拮抗类药物对精神分裂症治疗有效的观察而提出, 并获得了大量实验数据的支持, 因而成为精神分裂症病理原因最经典的解释。但必须指出, 解剖学研究中并没有发现多巴胺系统相关脑区和受体的病变, 提示多巴胺系统本身可能并非诱发精神分裂症的根本原因(Gothelf et al., 2000)。

近年来, 精神分裂症研究领域的另一个假说——大脑 GABA 系统缺陷假说逐渐引起了领域内研究者们的注意。其中, GABA 能的小清蛋白阳性(parvalbumin positive, PV+)的中间神经元独特的性质和作用而备受关注(Cohen, Tsien, Goff, & Halassa, 2015)。PV+神经元是一种快速放电的局部中间神经元, 其能够通过各种微环路构成的神经网络对同区域的锥体神经元及其他中间神经元进行调控(Hu, Gan, & Jonas, 2014; Tremblay, Lee, & Rudy, 2016), 还有证据表明, PV+神经元参与了突触可塑性(Caillard et al,. 2000; Donato, Rompani, & Caroni, 2013), 并在脑发育(尤其在视觉发育)关键期发挥了重要作用(Fagiolini et al., 2004; Katagiri, Fagiolini, & Hensch, 2007; Kuhlman et al., 2013; He et al., 2014; Gu et al., 2016)。近期许多研究表明, PV+神经元在精神分裂症中扮演了重要角色(Cohen et al., 2015; Steullet et al., 2017)。本文综述了目前 PV+神

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经元对精神分裂症影响的相关研究, 以期对了解该疾病的内在机制并开展进一步的研究提供借鉴。

2　PV+神经元的介绍

若以还原论的视角尽可能简单地描述大脑神经网络, 其主要由两种类型的神经元组成：提供兴奋性神经冲动的谷氨酸能主神经元(Glutamate principal neurons)和拥有抑制功能的 γ-氨基丁酸能中间神经元(GABAergic interneurons)。纵观全脑, 虽然 GABA 能中间神经元仅占神经元总量的 10%~20% (Freund & Buzsáki, 1996; Aika, Ren, Kosaka & Kosaka, 1994; Halasy & Somogyi, 1993), 但由于其多样化的形态结构与生理功能, 因而在调节、整合神经网络信号中发挥了极其重要的作用。此外, GABA 能中间神经元的功能受损也是导致各种遗传发育及精神类疾病的主要原因(Marín, 2012)。

90 年代以来, 很多实验室开始研究一类特定的中间神经元：快速放电的小清蛋白阳性表达中间神经元(the fast-spiking parvalbumin-positive interneuron)。小清蛋白作为具有保守结构的酸性蛋白超家族的一员, 是一种小分子量(一般为 9~11 kDa)的钙离子绑定蛋白(Calcium binding protein, CaBP)。PV 中间神经元可根据其形态分为多种亚型, 并分别与锥体神经元的特定部位形成突触。其中最常见的是篮状细胞(Basket cell)和吊灯状细胞(Chandelier cell), 前者约占 PV 中间神经元总量的 90%, 主要投射到锥体神经元的胞体和近端树突; 后者则只与锥体神经元的轴突起始部位形成突触。由于 PV+神经元的轴突所靶向的细胞结构是锥体细神经元对输入信息作出反应并发放动作电位的关键部位, 因此 PV+神经元对锥体神经元能否产生动作电位以及动作电位发放的时相起着重要的调控作用。

一般来说, PV 阳性神经元通常是 GABA 能的。Celio 和 Heizmann (1981)通过免疫荧光双标 GAD (一种 GABA 能神经元的免疫标记物)和 PV, 证实 PV 阳性的神经元分布和 GABA 能神经元的分布有很高的一致性, 在大脑皮层中, 几乎所有的 PV+神经元都是 GABA 能的, 同时, 70-80%的 GABA 能神经元含有 PV。在海马的 CA1 区, 11%的神经元是 GABA 能的, 而这些 GABA 能神经元中 24%是 PV+神经元(Bezaire & Soltesz, 2013)。然而近年来有越来越多的证据表明, 谷氨酸能的 PV 阳性神经元不仅存在, 而且在神经系统中扮演了重要角色。例如, 最近有研究证明上丘中表达的 PV 的兴奋性投射神经元是参与激发“战斗−逃跑”反应的关键神经元亚型(Shang et al, 2015)。

20 年前, 这种中间神经元的性质完全不为人知。20 年后, 受益于膜片钳、同步多细胞记录、光遗传、钙离子成像等等技术的广泛使用, 我们对 PV 中间神经元的认识变得比其他几种中间神经元要更多。它们不仅参与了基础的微环路功能, 例如前馈抑制和反馈抑制(Buzsàki & Eidelberg, 1981; Miles,1990; Pouille & Scanziani, 2001, 2004), 或 gamma 震荡波的产生(Bartos, Vida & Jonas, 2007; Cardin et al, 2009; Sohal, Zhang, Yizhar, & Deisseroth, 2009; Stark et al, 2013); 还参与了复杂的神经网络运作, 例如大脑发育“关键期”突触可塑性的调控(He et al., 2014)以及感知反应的增益调节(Hu et al., 2014)等等。此外, PV+神经元也在多种脑疾病中扮演重要角色(例如癫痫、自闭症、精神分裂症), 因此也是很多临床脑疾病的未来的治疗的潜在方向。

3　PV+中间神经元与精神分裂症

3.1　与精神分裂症相关的 PV+中间神经元变化

精神分裂症最显著表现就是前额叶(Lewis et al., 2005) 和海马 (Zhang & Reynolds, 2002) 的 GABA 系统的改变。具体表征有 GAD67 表达和 PV+神经元数量减少(Todtenkopf & Benes, 1998; Hashimoto et al., 2003)。例如, 在精神分裂症患者的尸检研究, 发现了几个脑区中 PV+神经元选择性地减少, 包括内侧前额叶(medial prefrontal cortex, mPFC)、丘脑、内嗅皮层(entorhinal cortex)和海马前部(Beasley & Reynolds, 1997; Bitanihirwe, Lim, Kelley, Kaneko, & Woo, 2009; Pantazopoulos, Woo, Lim, Lange, & Berretta, 2007; Zhang & Reynolds, 2002)。其中以海马的相关报道最为常见, Zhang 和 Reynolds (2002)甚至在精神分裂症患者海马的所有亚区都发现了 PV 中间神经元密度的降低, 而作为对照的另一种 GABA 能的中间神经元——Calretinin+神经元的密度则不受影响。近年来, 很多证据都将海马定位为精神分裂症发病的中枢, 甚至是始发脑区, 其他脑区的变化可能只是海马病变的次级效应。该理论认为, 海马前部 GABA

能中间神经元(主要是 PV+神经元)的功能失调极大地削弱了对该脑区的抑制控制，兴奋/抑制的平衡被打破，从而导致其活动水平异常增强(Behrens & Sejnowski, 2009; Lodge, Behrens, & Grace, 2009; Grace, 2012)。例如，对精分患者的功能性成像揭示了其海马的过度激活(Malaspina et al., 1999; Medoff, Holcomb, Lahti & Tamminga, 2001; Heckers, 2004; Schobel et al., 2009; Kraguljac, White, Reid & Lahti, 2013)。

PV 缺陷在精神分裂症的动物模型中也得到了印证。例如，在精神分裂症的 MAM 模型中，在母鼠怀孕第 15 天腹腔注射神经毒素甲基氧化偶氮甲醇(methylazoxymethanol, MAM)诱发子代出现精神分裂样症状，发现 MAM 注射会导致成年后的子代腹侧海马的的 PV+神经元特异性地丧失(Lodge et al., 2009)。此外，在精神分裂症的 polyribocytidilic (polyIC)模型(给怀孕 17 天的孕鼠注射 polyIC)中，也出现了 mPFC 和 vHPC 的 PV+神经元减少的现象以及安非他明诱发的运动增强(Meyer, Nyffeler, Yee, Knuesel & Feldon, 2008)。

此外，包括精神分裂症在内的许多精神疾病还伴随着异常的神经发生(neurogenesis)，由于抑制性神经递质 GABA 在神经发生的各个阶段均发挥着重要的作用，包括 PV+神经元在内的 GABA 能中间神经元的缺陷很有可能是导致此类疾病中神经发生异常的原因。有文献报道在海马的齿状回颗粒细胞下层(subgranular zone,SGZ)的 PV+神经元能够调控新生神经元的分裂成熟、树突的发育及突触整合(Ge et al., 2006; Song et al., 2013)。Song 等人(2013)利用光遗传技术发现 PV+神经元特异地对 I 型细胞的增殖和自我更新具有调控作用。此外，PV+神经元还能影响新生神经元的存活，Wang 等(2014)发现敲除 PV 阳性中间神经元的淀粉样前体蛋白(amyloid precursor protein, APP)可以影响突触周围 GABA 的含量，进而减少海马齿状回区新生颗粒细胞(DGCs)的存活。

因此，PV+神经元功能功能的健全与否关系到中枢神经系统的兴奋/抑制平衡的维持和神经发生的正常进行，因而成为包括精神分裂症在内的众多精神病领域的热门研究对象(Kobayashi & Buckmaster, 2003; Gogolla et al., 2009; Burguière, Monteiro, Feng & Graybiel, 2013; Steullet et al., 2017)。下文将以精神分裂症中 PV+神经元的异变为锚点，结合精分研究领域中最常见的三种病理表征(NMDA 受体缺陷、gamma 波异常和氧化应激)，进一步介绍 PV+神经元在精神分裂症中的作用。

3.2 精神分裂症的 gamma 波异常与 PV+神经元缺陷

Gamma 波缺陷常见于精神分裂症的相关研究中，是其重要的症状表型之一。在对精神分裂症患者的研究中，Gamma 波异常的具体表现形式呈现多样性，包括波幅降低(Haig et al., 2000; Kwon et al., 1999)和增加(Demiralp et al., 2006; Flynn et al., 2008; Barr et al., 2010)，以及特定频段的 gamma 波减少(Spencer et al., 2003; Spencer, Niznikiewicz, Shenton, & McCarley, 2008; Uhlhaas et al., 2006)等等，考虑到上述研究都是事件相关的，出现这种多样性可能是所采用的认知任务本身的不同所导致的(Hunt, Kopell, Traub, & Whittington, 2017)。同样的，精神分裂的易感基因模型也表现出 gamma 波缺陷，比如 Neuregulin，erbB4 和 calcineurin 等基因的突变在诱发小鼠精分样行为的同时，伴随了 gamma 波的增加(Del Pino et al., 2013; Fisahn, Neddens, Yan, & Buonanno, 2008; Suh, Foster, Davoudi, Wilson, & Tonegawa, 2013)。

由于 Gamma 神经振荡的产生需要对主神经元产生强烈的协同性抑制(Gonzalez-Burgos & Lewis, 2008)，精神分裂中常见的 GABA 神经传递的缺陷被认为是导致 gamma 异常的潜在机制(Lewis, Curley, Glausier, & Volk, 2012)；鉴于 PV+神经元是 gamma 荡波形成的关键因素(Bartos et al, 2007; Cardin et al, 2009; Stark et al, 2013)，且又是在精神分裂症中突触传递功能受损最严重(荧光原位杂交中检测到丢失 GAD67 mRNA 最多)的 GABA 能中间神经元亚型(Hashimoto et al., 2003)，提示二者在精神分裂症中存在紧密的联系，并得到了相关实验证据的支持——在精神分裂症的动物研究中，就多次观察到 PV 表达和 gamma 波的同步减少(Cunningham et al., 2006; Lodge et al, 2009; Steullet et al., 2010)。因而大量的研究者认为，精神分裂症中常见的 PV+神经元受损或许能为该疾病状态下执行认知任务时不正常的 gamma 波提供合理的解释(Lewis et al., 2012; Volk, Gonzalez-Burgos, & Lewis, 2016; Uhlhaas & Singer, 2010)。譬如说，Kim, Ährlund-Richter, Wang, Deisseroth 和 Carlén(2016)揭示了内侧前额叶的 PV+神经元介

导的 gamma 波是产生自上而下注意的关键因素，可能是包括精神分裂症在内的多种精神疾病中广泛存在的注意力缺陷的内在病理机制。值得注意的是，前文提到 PV+神经元可根据结构分为两种亚型，有研究者认为是 PV+神经元的篮状细胞，而不是吊灯状细胞的突触前或突触后的变化导致了精神分裂中的 gamma 波的紊乱和认知损伤(Lewis et al., 2012; Gonzalez-Burgos & Lewis, 2012)，但由于目前尚无法在细胞层面对这两种 PV+神经元亚型进行分别的操纵，因此还没有最直接的证据。

3.3 精神分裂症的 NMDA 受体缺陷与 PV+神经元缺陷

NMDA 受体缺陷假说也是精神分裂症的经典假说之一，自 Luby 等人(1959)发现 NMDA 受体拮抗剂 PCP (phencycline)可以在正常人身上引发类似精神分裂症样的行为表征后，该假说在精神分裂症领域一直备受关注。在此之后，包括 PCP 在内的很多 NMDA 受体拮抗剂(例如 APV, CPP, MK-801 和 Ketamine)陆续被发现能够引发精神分裂症样症状，并被应用于精神分裂症研究的动物造模中(Javitt & Zukin, 1991; Krystal et al., 1994; Olney & Farber, 1995)。

很多证据表明 NMDA 受体与 PV+神经元之间存在密切的关系。NMDA 受体被发现能够干预中枢神经系统中 GAD67 和 PV 的表达(Kinney et al., 2006; Romón & Adell, 2011; Abekawa, Ito, Nakagawa, & Koyama, 2007)，影响 PV+神经元的抑制性突触传递(Zhang, Behrens, & Lisman, 2008)，还可以调节其放电特性(Albéri, Lintas, Kretz, Schwaller, & Villa, 2013)与突触可塑性(Caillard et al., 2000)。此外，有证据表明 NMDA 受体的 NR2A 亚基在 PV+神经元中可能扮演重要角色，通过单细胞分离 mRNA 测定不同类型细胞中 NR2A/NR2B 的比率，发现 PV+神经元中 NR2A/NR2B 的 mRNA 表达量之比是锥体神经元的五倍，进一步的药理实验揭示了 NR2A 而不是 NR2B 的选择性拮抗剂减少了 PV 的表达(Kinney et al., 2006)。

考虑到精神分裂症中普遍报道的 PV+神经元缺陷，上述研究暗示 NMDA 受体受损可能是导致精神分裂症中 PV+神经元结构和功能异常的关键因素。换句话说, PV+神经元受损在精神分裂症中可能是 NMDA 受体功能失调的二级效应。NMDA 受体功能不全导致 PV+神经元更难以被兴奋，由于 PV+神经元是重要的抑制性神经元，其在局部神经微环路中角色的缺失会直接引起锥体神经元的兴奋性的增加，使得神经网络去抑制，从而导致大脑兴奋/抑制水平的失衡，进而引发精神疾病(Cohen et al., 2015; Lisman et al.,2008)。最直观的证据来自转基因动物的研究，例如，Belforte 等人(2010)发现，在敲除 NMDA 受体诱发出 GAD67 和 PV 表达下调的同时，动物还表现出精神分裂症样的行为。而在 PV+神经元中特异性地敲除 NR1 亚基的基因(使得 NMDA 受体无法在 PV+神经元中表达)，会导致该转基因动物表现出脑电波异常(Carlen et al., 2012; Korotkova, Fuchs, Ponomarenko, von Engelhardt, & Monyer, 2010; Billingslea et al., 2014; Gonzalez-Burgos & Lewis, 2012)，认知功能受损(Carlen et al., 2012; Korotkova et al., 2010)，社交障碍(Saunders et al., 2013; Billingslea et al., 2014)等精神分裂症中常见的症状表现。

与此同时，精神分裂症中 Gamma 波的异常也间接佐证了上述推测。前文提到, PV+神经元是参与 Gamma 波形成的必要条件(Sohal et al., 2009; Bartos et al., 2007; Cardin et al, 2009; Stark et al, 2013)，而 gamma 波异常又是精神分裂症的常见表型(Bartos et al., 2007; Klausberger & Somogyi, 2008; Cardin et al., 2009; Lodge et al., 2009)。在此基础上，一些研究者采用药理阻断或者基因删除的方式来操控 PV+神经元中的 NMDR 受体，成功干扰了 Gamma 波(Lisman et al., 2008; Gonzalez-Burgos & Lewis, 2012; Korotkova et al., 2010; Carlen et al., 2012; Kocsis, 2012)，证明了 PV+神经元中的 NMDR 受体的确在 gamma 波的形成中起到重要作用，其功能紊乱可能是精神分裂症中 gamma 波异常的潜在病理原因之一。值得注意的是，上述实验结果可能存在发育阶段的特异性：只表现在出生后早期删除 NMDA 受体的动物身上，而不能表现在青春期后删除 NMDA 受体的动物上(Belforte et al., 2010)；这说明 NMDA 受体不仅参与协同局部微环路的神经振荡，而且对 PV+神经元生理功能的发育成熟是必不可少的(Cohen et al., 2015)。

3.4 精神分裂症氧化应激上调与 PV+神经元缺陷

氧化应激(oxidative stress)，指的是人体在异常状态下，氧化和抗氧化机制失衡，导致过量的自由基对神经元和大脑的损害作用，它与神经炎

症关联紧密。而在精神分裂症中，大脑的氧化应激/氧化还原机能的紊乱已被多次证明，并逐渐成为领域内的共识(Do, Cabungcal, Frank, Steullet, & Cuenod, 2009; Flatow, Buckley, & Miller, 2013; Yao & Keshavan, 2011; Steullet et al., 2017)，最近，有研究者(Kim et al., 2016)利用磷磁共振波谱(Phosphorus magnetic resonance spectroscopy, P-MRS)进行 NAD+/NADH 的检测，首次在人类身上证明了精神分裂症的抗氧化机能失调。大脑抗氧化机能的失调包括脑内谷胱甘肽(glutathione, GSH)的减少(Do et al,2009)，由于 GSH 是主要的内源性抗氧化剂和氧化还原反应的调节剂，其合成缺陷会导致小鼠腹侧海马的 CA3 和齿状回的 PV+神经元选择性地减少，并伴随着 β/γ 神经震荡的减少，并引起相关的精神病样行为症状(Steullet et al., 2010)。

精神分裂症中的 PV+神经元损伤和过度的氧化应激之间存在重要联系，许多精分相关的环境风险因素/早期应激源能够干扰抗氧化系统，增加氧化应激(Do et al., 2009)和神经炎症(Brenhouse & Andersen, 2011; Gárate et al., 2013; Kaur, Rathnasamy, & Ling., 2013)，并且减少前额叶和海马的 PV 表达(Dell'Anna, Geloso, Magarelli & Molinari, 1996; Harte, Powell, Swerdlow, Geyer, & Reynolds, 2007; Meyer et al, 2008; Brenhouse & Andersen, 2011; Komitova et al., 2013)。虽然上述研究并没有阐明二者之间的因果关系，但种种迹象表明，氧化应激是导致 PV+神经元损伤的重要原因。

首先，在时间顺序上，氧化应激发生在 PV+神经元呈现缺陷之前(Steullet et al., 2010)；其次，在多种精神分裂的动物模型中都证实了，抗氧化应激药物对 PV+神经元的起到了有效的保护作用(Cabungcal, Steullet, Kraftsik, Cuenod & Do, 2013; Behrens et al., 2007; Schiavone et al., 2009; Cabungcal et al., 2014; Jiang, Rompala, Zhang, Cowell, & Nakazawa, 2013)。为了进一步验证氧化应激诱发的 PV+神经元缺陷是否是精神分裂症的普适性病理原因，最近 Steullet 等人(2017)在多达 9 种精神分裂症模型动物(大体可分为基因模型、损毁模型、药理模型和环境模型)的前扣带回(ACC)中免疫共染了 PV、PNN (环神经元周围网, Perineuronal nets)和 8-oxo-dG (氧化应激的标记物)，结果发现，除了两种模型动物没有表现出以上三种标记物的任何改变，在其余的动物中，PV+神经元缺陷必然伴随着不同程度的氧化应激。综上，我们可以得出结论，由过度的氧化应激引发的 PV+神经元缺陷在精神分裂症中是一个普遍现象，它可能是该疾病的大多数易感因素(包括药物、环境、基因等)最终诱发精分表型的“必经之路”。

然而，上述结论引申出了另一个重要的问题：过度的氧化应激是如何选择性地损伤 PV+神经元，而不是其他神经细胞呢？精神分裂症中可普遍观察到的 PNN 的异常变化为我们提供了参考答案(Steullet et al., 2017; Mauney et al., 2013; Pantazopoulos, Woo, Lim, Lange, & Berretta, 2010)。PNN 是一种具有细胞特异性的胞外基质(extracellular matrix)结构，它主要包裹在 PV+神经元的胞体和近端神经突(Rossier et al., 2015)。有证据表明 PNN 是保护 PV+神经元不受氧化应激损伤的重要结构(Cabungcal et al., 2013)，因此精神分裂症中的 PV+神经元缺陷可能是由于 PNN 异常导致 PV 神经元失去对氧化应激的防御机制所引发的次级效应(Cohen et al., 2015)。

4 总结和展望

尽管精神分裂症已经被研究多年，相关假设和实验结果层出不穷，然而我们对其病理机制仍然不是很清楚。在其中，PV+神经元缺陷只是该疾病众多神经生理变化的其中一隅，然而近年来的种种实验证据都最终指向了 PV+神经元异常，提示 PV+神经元在该疾病中可能扮演重要角色。因此，本文立足于 PV+神经元的基本结构功能及其在精神分裂症中的缺陷，对其在精神分裂症中的改变及其相关的实验证据进行了综述，以期为相关研究的深入探索提供借鉴和支持。

包括 PV+神经元在内的中间神经元之间存在着复杂而重要的相互作用，它们和主神经元一起构建了精细的神经微环路系统，共同决定了大脑认知功能的正常运行(Wolff et al., 2014; Markram et al., 2004)。在其中，PV+神经元是被研究得最多的一种 GABA 能中间神经元，这一方面是因为它是皮层中最多的中间神经元(占中间神经元总数的 40%) (Tremblay et al., 2016)，另一方面则是因为其快速高频放电的特性而在电生理记录中更具有区分度。而在精神分裂症中，PV+神经元也比其他中间神经元受到了更多的关注，这种偏爱的理

由其实依然基于上述两个方面，这种惯性使得大多数精神分裂症研究中所指出的 PV 缺陷的结果缺乏特异性。尽管有充足的证据表明，精神病患者的大脑表现出 PV、SOM 和 CCK 表达的同步下调，暗示了多种中间神经元亚型在该疾病中的参与(Morris, Hashimoto & Lewis, 2008; Konradi et al., 2011)，但我们仍然不清楚其它中间神经元(比如 SOM+神经元，VIP+神经元)是如何参与了精神分裂症，是否也和 gamma 缺陷，NMDA 受体异常和氧化应激，以及其它认知和生理上的病变存在某种联系。鉴于以上原因，未来的研究应试图阐明不同的中间神经元亚群在精神分裂症中的潜在机制和作用权重。

与此同时，围绕 PV+神经元突触前后相关受体为靶点进行的抗精神病药物的开发也在进行中，目前的关注点主要集中在 $GABA_A$ 受体上，尤其是 α1-6 亚基(Gill & Grace, 2014)。在新皮层和海马中，含 α5 亚基的 $GABA_A$ 受体位于 PV+神经元突触后，影响 PV+神经元对锥体神经元的调控；而含 α1 和 α2/3 亚基的 $GABA_A$ 受体则主要分布于 PV+神经元突触前，接收来自其他神经元的抑制性信号(Ali & Thomson, 2007)。其中又以 GABAA 受体 5α 亚基最为瞩目，已有药理实验表明 5α GABAA 受体激动剂能在一定程度上扭转精神分裂症相关的认知缺陷(Featherstone, Rizos, Nobrega, Kapur, & Fletcher, 2007; Gill, Lodge, Cook, Aras, & Grace, 2011; Gill & Grace, 2014)。尽管如此，目前尚未有此类药物通过临床实验的报道，但这仍不失为新的抗精神病药物开发的一个方向。

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Roles of impaired parvalbumin positive interneurons in schizophrenic pathology

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Abstract: Schizophrenia is a severe mental disorder typically began in late adolescence or early adulthood. To date, the cause of schizophrenia remains largely unclear. The classical dopamine hypothesis of schizophrenia is now thought to be sided. Meanwhile, the involvement of impaired Parvalbumin positive interneurons (PV+ neurons) in the pathological mechanism of schizophrenia has been realized and received increasing attention. Generally, PV+ cells is a kind of inhibitory, fast-spiking interneurons, which had been demonstrated to be involved in synaptic plasticity, excitation/inhibition balance and neurogenesis. In schizophrenia, abnormal PV+ neurons has been commonly found in patients and relevant animal models., In this article, we reviewed the roles of deficits of PV+ neurons in schizophrenic pathology combined its principal phenotypes including defective NMDA receptors, abnormal gamma oscillation and oxidative stress, hoping to contribute to further investigation and development of new drugs.

Key words: schizophrenia; interneurons; NMDA receptors; oxidative stress.